NECROTIZING ENTEROCOLITIS*

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IN 1891 Genersich[1] reported the case of a 45-hour-old premature infant who had vomiting, cyanosis, and abdominal distention; death occurred within 24 hours. At postmortem examination the infant was found to have inflammation of the ileum and an area of perforation. No cause could be determined. Subsequent observers have reported similar cases in increasing numbers and have labeled the disease "necrotizing enterocolitis." This entity has been characterized by vomiting, abdominal distention, and bloody stools; roentgen studies have revealed evidence of pneumatosis intestinalis, pneumoperitoneum, or gas in the main portal vein. Up to the present time slightly more than 100 cases have been reported. Approximately 30% of the patients have survived. It is the purpose of this paper to present the case of a child who survived and to discuss the disease.

CASE REPORT

On September 14, 1969 an infant weighing 1,219 gm. was born to a 27-year-old Negro primigravida after an uneventful 30-week gestation and delivery. During the first 24 hours the infant had frequent attacks of cyanosis, which were treated with 40% oxygen. At 27 hours she was transferred to the Neonatal Intensive Care Unit of the Bronx Municipal Hospital Center. On admission she was noted to be a pink, vigorous infant not in respiratory distress; there were occasional apneic episodes, which responded to stimulation. Vital signs: pulse 112/min., respirations 48/min., temperature 36.4°C.; weight 1,200 gm. The physical examination was unremarkable, except for the absence of ear cartilage and breast tissue; neurological findings were compatible with a gestational age of 29 to 30 weeks. At the time of admission the following laboratory observations were made: hemoglobin 20.2 gm.%, hematocrit 59%, white-blood count 7,1500/mm.^{3} with normal differential

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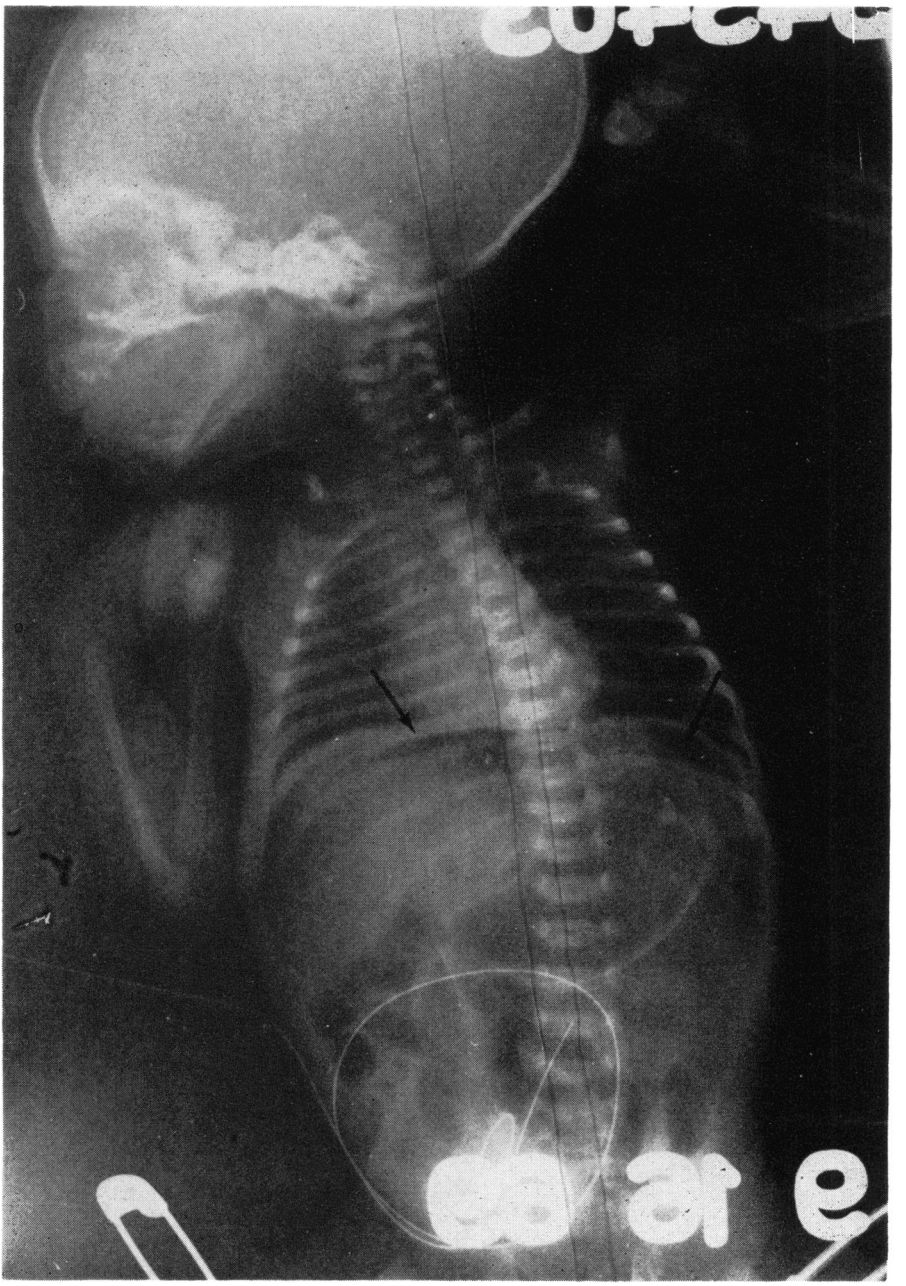

Fig. 1. Supine x ray of the abdomen at 52 hours of age; gas under the diaphragm and overlying the liver.

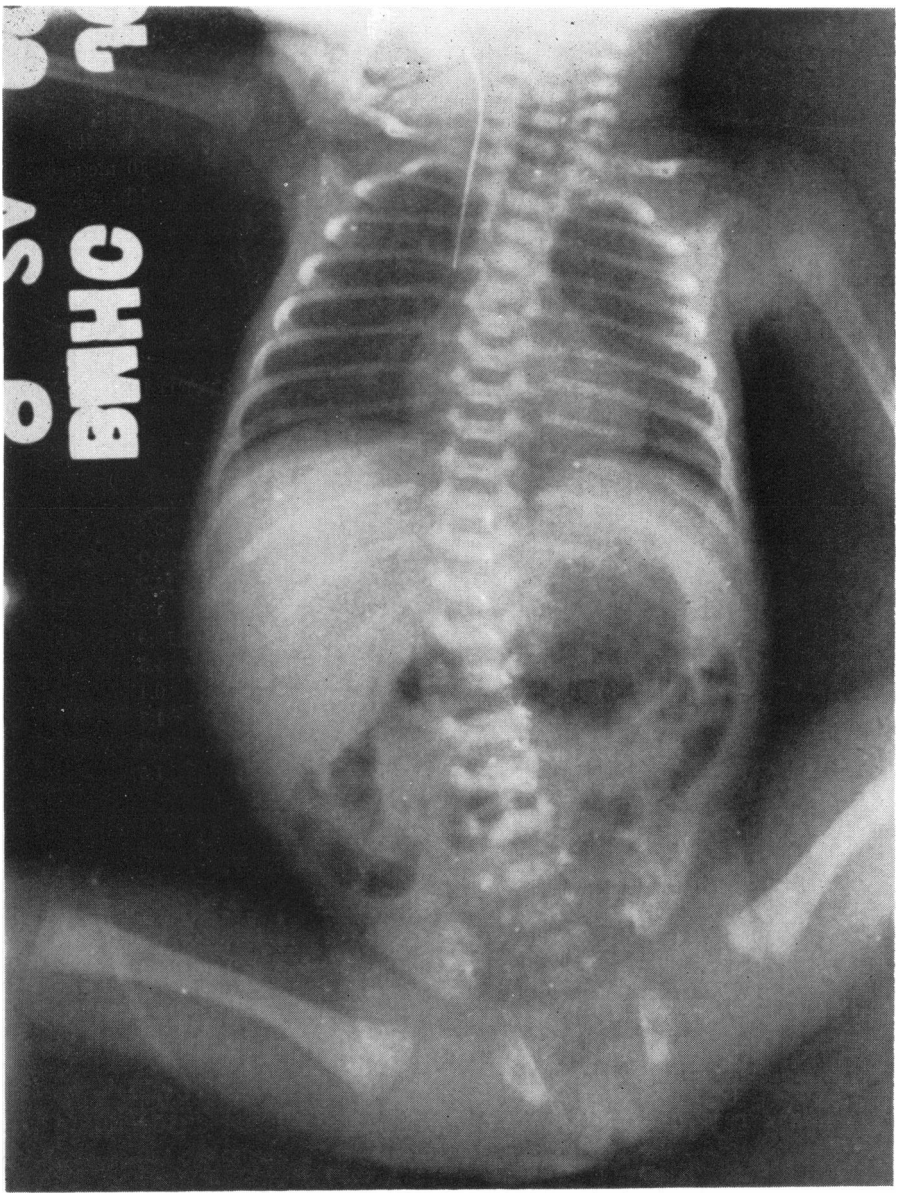

Fig. 2. X ray of the chest with catheter extending from the external jugular vein into the superior vena cava for intravenous hyperalimentation.

TABLE I. COMPOSITION OF INFUSATE (SOLUTION No. 1)

Fibrin hydrolysate (5%)—dextrose (5%)*	375 cc.
Dextrose (50%)*	200 cc.
Vitamin C	500 mg.
Berocia C†	1 cc.
Sodium heparin (1000u./ml.)	500 units
Potassium chloride	10 meq.
Sodium chloride	10 meq.

*Abbott Laboratories, N. Chicago, Ill.
†Roche Laboratories, Nutley, N.J.

TABLE II. COMPOSITION OF INFUSATE AS SUGGESTED BY FILLER, ET AL.[8] (SOLUTION No. 2)

Constituent	*Amount (cc.)*
Fibrin hydrolysate (5%)—dextrose (5%)*	1,000.0
Dextrose (50%)*	500.0
Potassium chloride (2 mEq./ml.)	15.0
Magnesium sulfate (10%)	1.25
Calcium gluconate (10%)	15.0
Phytadione (Agua Mephyton) 0.2 mg./ml.)	1.5
Vitamin B_{12} (100 m./cc.)	0.1
Multivitamin infusion (MVI)†	1.5
Sodium chloride (2.5 mEq./ml.)	6.0
Sodium heparin (1,000 u./ml.)	1.5

*Abbott Laboratories, N. Chicago, Ill.
†U.S. Vitamins and Pharmaceutical Corp., New York, N. Y.

and 25 nucleated RBC/100 WBC; blood type O-positive, Coombs test negative, urine normal, blood sugar 110 mg.%. Shortly after admission a catheter was placed in an umbilical artery and an infusion of 5% dextrose and water was begun. The patient was then placed in 60% oxygen; after 15 minutes arterial blood was drawn from the catheter for studies. The results were: *p*H 7.35, P_{CO_2} 45 mm. Hg, P_{O_2} 240 mm. Hg, total CO_2 24.5 meq./l, bicarbonate 23.5 meq./l., and a base deficit of 2.5 meq./l. The concentration of oxygen was then reduced. Episodes of apnea continued, but became less frequent. At 38 hours the infant was doing well and was placed in room air; half-strength Alacta feedings were started. At approximately 52 hours of

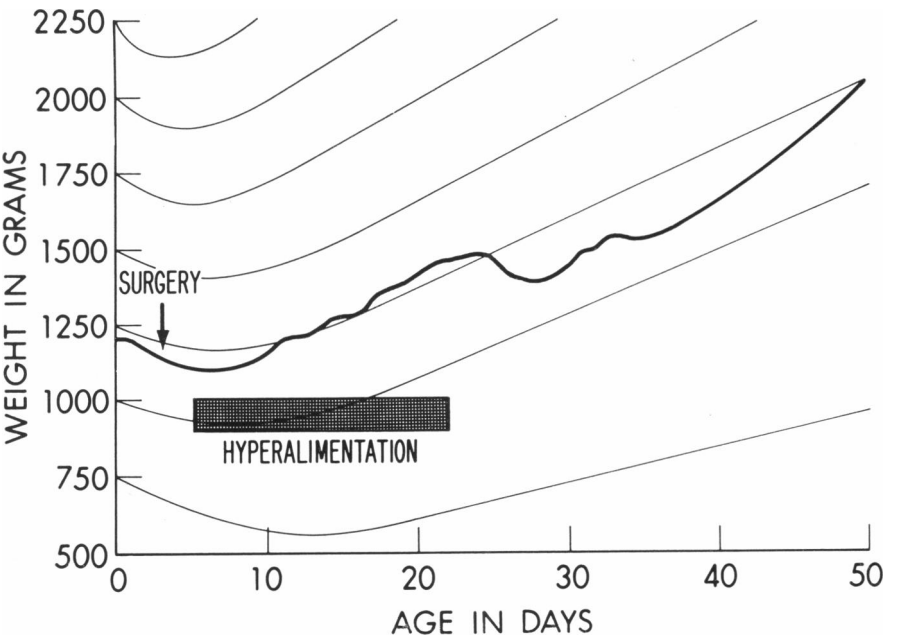

Fig. 3. Growth chart of premature infant illustrating the gain in weight during intravenous hyperalimentation and subsequent transient loss when this treatment was discontinued.

age the child developed abdominal distention. Aspiration of the stomach yielded a small amount of undigested formula. X-ray examination of the abdomen revealed the presence of a large pneumoperitoneum (Figure 1). Surgical exploration disclosed perforation of the ileum and changes compatible with necrotizing enterocolitis. Twenty-two centimeters of ileum were resected and an end-to-end anastomosis was performed. After operation the infant was given penicillin, kanamycin, and intravenous fluids. Serial roentgen examinations of the abdomen performed at intervals of 12 hours showed no further abnormalities. At 74 hours the child was seen to be jaundiced. A right internal jugular cutdown was placed, according to the method of Dudrick et al.[2] (Figure 2). Shortly thereafter the first of four exchange transfusions was performed for idiopathic hyperbilirubinemia. After the initial exchange transfusion an intravenous infusion of half-strength Aminosol mixture at a rate of 90 cc./kg./day (Table I) was started and a millipore filter*

*Swinnex-25 Filter Unit, Type G.S. Filter (0.22), Millipore Corp., Bedford, Mass.

TABLE III. LABORATORY FINDINGS DURING PARENTERAL FEEDING

Date	9/17	9/18	9/19	9/20	9/21	9/24	9/29	10/1	10/6	10/12
Postoperative day	0	1	2	3	4	7	12	14	19	25
NA+ (mEq./L)	144	140	135	141	141	142	138	136	130	136
K+ (mEq./L	5.9	5.0	3.1	3.3	6.0	5.2	5.7	5.6	5.2	4.6
Cl^- (mEq./L)	109	107	103	105	102	108	109	97	98	90
CO_2 (mEq./L)	20.1	21.2	28.7	32.0	26.6	23.6	23.6	20.8	17.1	25.9
Bun (mg./100 cc)	—	43	39	26	23	9	—	17	12	—
Sugar (mg./100 cc)	—	40	110	85	—	130	85	90	50	65
Solution No. 1*						9/26				
Solution No. 2†									10/6	

*Aminosol, Abbott Laboratories, North Chicago, Ill.
†As per Filler et al.[3]

was placed in line. On the second postoperative day a full-strength solution was given and the volume was gradually increased to 135 cc./kg./day. The child was also given biweekly transfusions of whole blood to maintain the hematocrit and to replace trace elements. On the 9th postoperative day the Aminosol solution was changed to that suggested by Filler et al.[3] (Table II). No stools had been passed by the 13th postoperative day; x-ray studies of the upper gastrointestinal tract showed no evidence of obstruction. A normal stool was passed 24 hours later. On the 16th postoperative day oral feedings were reinstituted without difficulty and intravenous fluids were decreased. By the 19th day the patient received Nutramigen and the infusion was discontinued. The remainder of the hospital course was uncomplicated, except for a transient loss of weight (Figure 3). The patient was discharged at 60 days of age with a weight of 2,320 gm. At present she is growing well and has had no further gastrointestinal dysfunction.

At no time during the hospital course were there problems with electrolytes or blood sugar (Table III).

DISCUSSION

Necrotizing enterocolitis is found mainly in premature infants. In most large series reported 70 to 90% of infants affected weighed less than 2,500 gm.; the majority of these weighed less than 1,600 gm. [4-8] Up to 60% also had a history of various complications or difficulties in the immediate prenatal period.[4,5,7,9] The maternal complications con-

sisted of either premature rupture of membranes, prenatal fevers, or infected amniotic fluid, while the neonatal difficulties consisted of low Apgar scores, minor apneic episodes, cyanosis, idiopathic respiratory distress syndrome, or exchange transfusion.

The infants seem to do well for the first two to five days despite the problems previously mentioned. Then they experience the insidious onset of vomiting associated with delayed gastric emptying. The episodes of apnea tend to recur or increase in severity.[4] Chest x rays are generally normal. The symptoms are followed by abdominal distention and by an increase in the vomiting; the vomitus is now bile-stained. The stools are bloody and often loose.[4,7,9] During this phase of the illness the findings revealed on x-ray examination of the abdomen are variable. In most reported cases the subsequent course has been fulminating. The infant appears lethargic, has increasing apneic episodes, becomes jaundiced, enters a state of shock resembling that seen with sepsis, and dies shortly thereafter despite all modes of treatment.

Early in the illness the roentgen findings resemble those of obstructive gastrointestinal disease (Figure 4) and include increased intraluminal air, dilated loops of bowel, and frequently air-fluid levels. If these observations are made in a premature infant who has the previously mentioned signs and symptoms, the diagnosis of necrotizing enterocolitis should be entertained. Intramural gas (Figure 5) is found late in the illness but may occur early. This may present as small curvilinear collections of extraluminal air, which parallel the loops of bowel, or as bubbly extraluminal collections of gas (Figure 6). Often the latter constitute the only abnormality noted. The gas produces a frothy appearance and may be mistaken for feces mixed with air. Because of the subtle nature of this finding serial x rays should be made at intervals of four hours in both the prone and supine positions, progressive changes being noted carefully. The etiology of pneumatosis is unknown, and it has been attributed to a disruption of necrotic mucosa with subsequent submucosal dissection by intraluminal gas.[4] Another explanation is that of submucosal invasion by gas-producing bacteria, but this has not been borne out by bacteriologic investigation.[6,10,11]

Pneumoperitoneum and gas in the main portal vein are late events and have been associated with a very high mortality.[7,12,13] The first report of gas in the portal vein was by Wolfe and Evans;[12] all

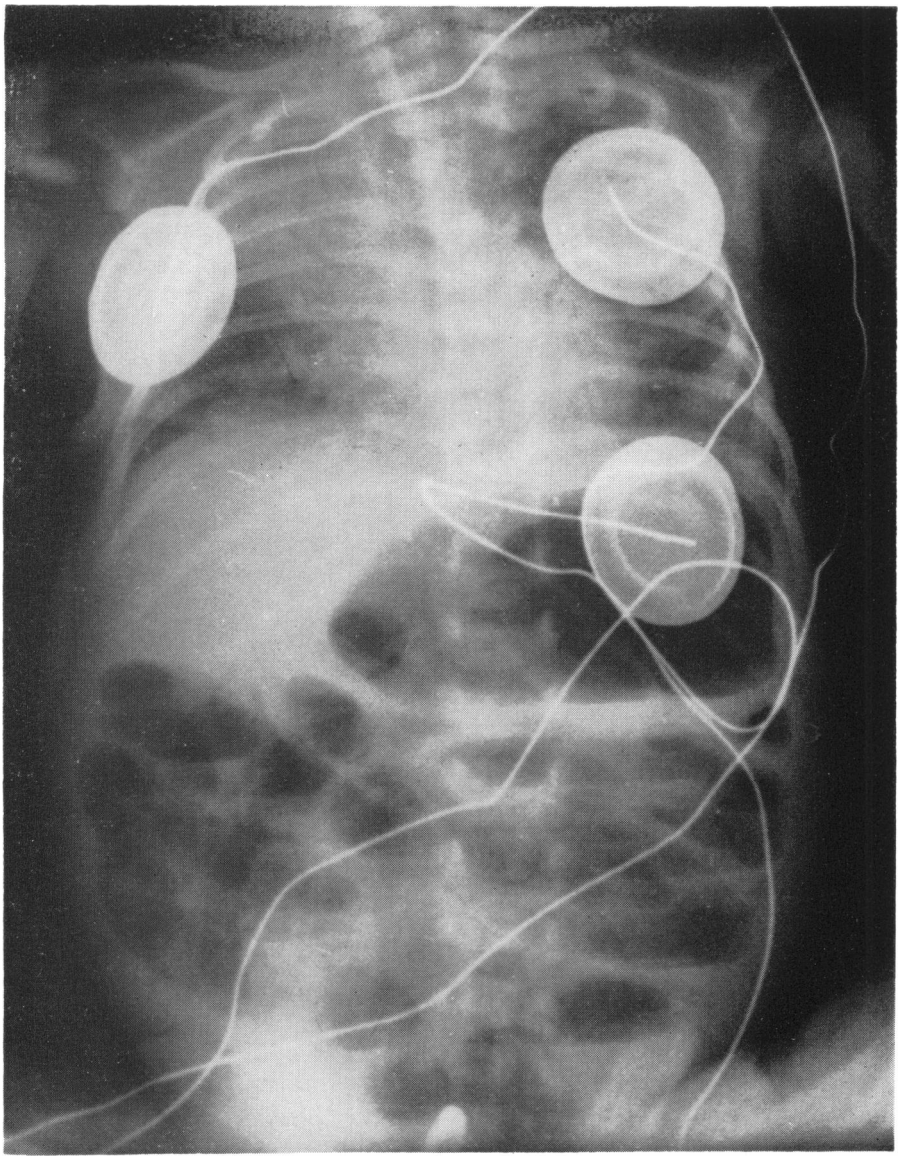

Fig. 4. Prone x ray of the abdomen in a premature infant who went on to develop necrotizing enterocolitis with pneumoperitoneum. Note increased intraluminal gas and several dilated loops of bowel.

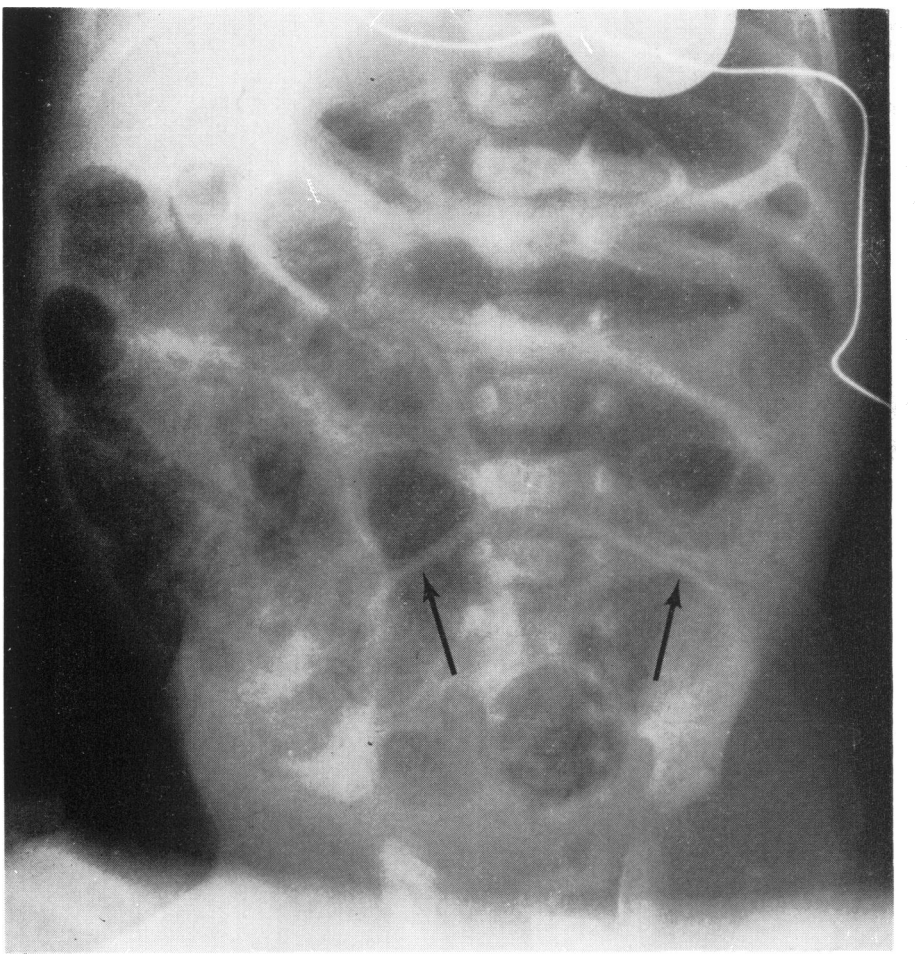

Fig. 5. Pneumatosis intestinalis presenting as curvilinear collections of extraluminal gas in a premature infant who later developed pneumoperitoneum.

six of their patients died. The following year Miskin et al. reported six more cases; of the four survivors two had received medical therapy only.[13] Though the gravity of the situation is much increased when either pneumoperitoneum or gas in the portal vein is present, one must remember that the disease is not always fatal, as our case shows.

At autopsy and in surgical specimens the microscopic findings have been nonspecific. The lesions have been found predominantly in the lower ileum, cecum, and the ascending colon. The early changes con-

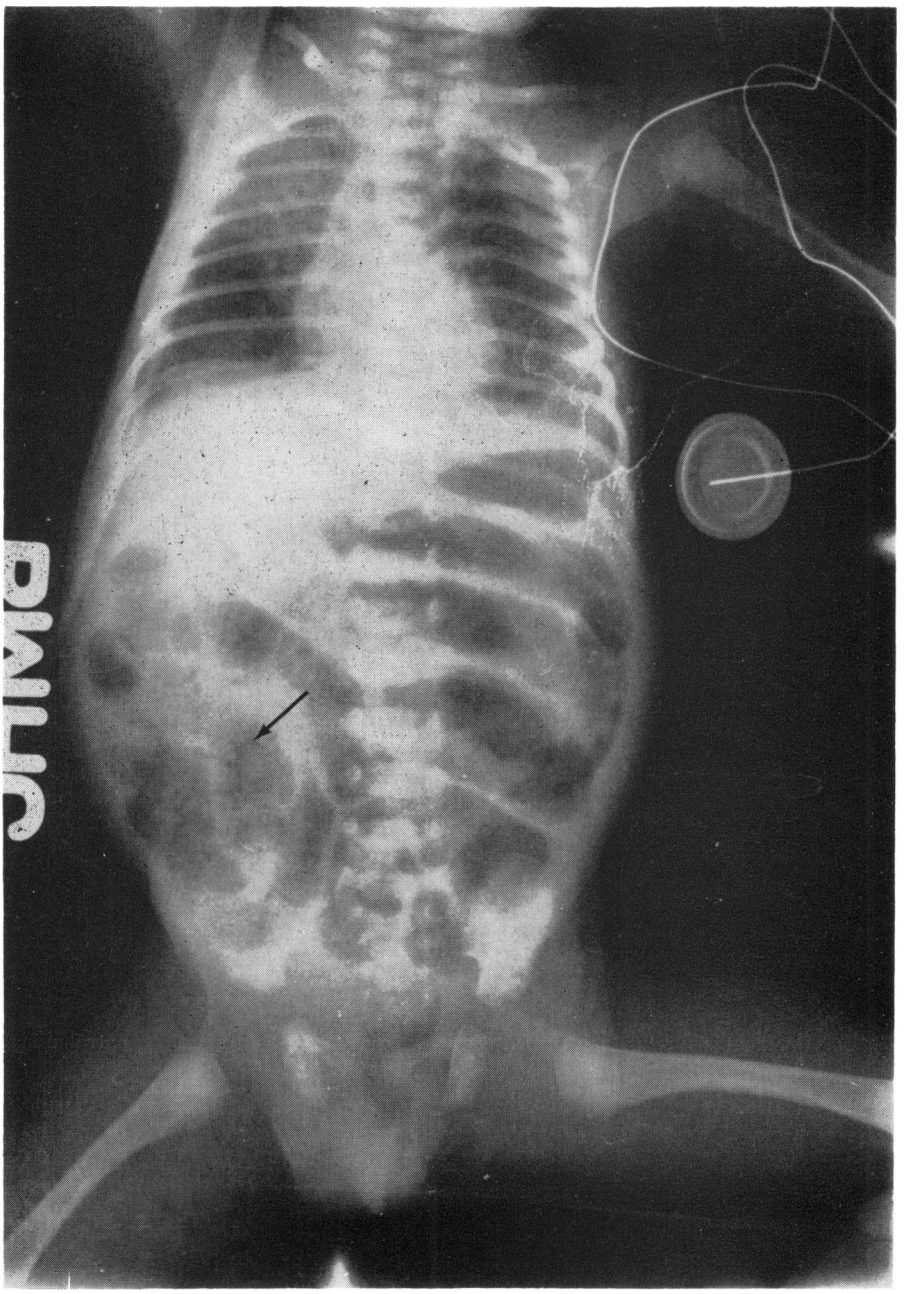

Fig. 6. Bubbly collections of extraluminal gas which represent a form of pneumatosis intestinalis and may be mistaken for feces mixed with gas. This infant later developed pneumoperitoneum.

sist of broadening of the mucosal villi with dilation of venules and capillaries, along with moderate infiltration by mononuclear cells. In later lesions the tissue is markedly friable; there is hemorrhage in the lamina propria, sloughing of mucosa, perforations, and an overlying pseudomembrane.[4,9] There is no evidence of vasculitis, thrombosed vessels, or aganglionosis, and no bacteria have been seen or cultured from lesions.

In the treatment of this disorder early recognition is crucial, and should be followed by prompt initiation of gastrointestinal decompression. Antibiotic therapy should include coverage for enteric organisms. The usual supportive measures should be used. Surgical consultation should be obtained immediately because of the frequently rapid progression to perforation. Serial x-ray films of the abdomen should be observed closely for extension of intramural gas or for other signs of progression. If during the ensuing 24 to 48 hours the infant's condition deteriorates or there are signs of radiologic progression, early surgical intervention is indicated and may lead to resection of variable lengths of bowel with ileostomy or colostomy. This course was followed by Stevenson et al.[4] in 21 cases; 67% survival was obtained and may be compared with the 11% reported by Mizrahi[5] in a series in which an operation was performed only when there was evidence of perforation. In the former series nine out of 12 infants who required operation lived; this represented 64% of the survivors. None of the infants reported by Mizrahi who underwent operation survived.

In infants requiring operations antibiotics should be continued for at least seven to 10 days in the postoperative period, and serial roentgen examinations should be made for 24 to 48 hours in order to determine further extension of the disease. In infants who have had extensive disease that required large resections of bowel or in those in whom the extent of the disease is questionable at the time of operation, hyperalimentation may be life-saving.[2,3] A barium enema should be planned a few weeks after recovery for those who survive after medical therapy, since there have been reports of intestinal obstruction after recovery.[11,14]

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